Title: James Lind Alliance research priorities: Should diet and exercise be used as an alternative to drugs for the management of Type 2 diabetes or alongside them?

Running title: Lifestyle vs drugs

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Novelty statement

- Interactions between physical activity and glucose lowering medications have been observed but are not well understood and there is little research into the interactions between medication and overall diet patterns.
- Few interventions compare lifestyle with drug therapy or control for medication use. At present available evidence indicates that most people will eventually need drug therapy in addition to lifestyle.
- There is little evidence for how best to support people in maintaining weight loss or physical activity for the long-term. Improving maintenance strategies may help more people delay or prevent medication use.

James Lind‡ Alliance research priorities: Should diet and exercise be used as an alternative to drugs for the management of type 2 diabetes or alongside them?

Abstract

Aims

The aim is to review evidence on whether diet and exercise should be used as an alternative to drug therapy for the management of type 2 diabetes or alongside.

Method

We present a narrative review that draws on evidence from other systematic reviews and meta-analyses, narrative reviews, trials and cohort studies. We focussed mainly on glycaemic control rather than control of blood pressure or cholesterol.

Results

Good quality dietary advice that results in weight loss of >5% and physical activity interventions of >150mins/week moderate to vigorous physical activity combined with resistance exercise can produce improvements to HbA1c similar to that produced by the addition of glucose lowering drugs. These improvements can be seen at all stages of the disease. There are recognised interactions between glucose lowering drugs and physical activity which may not be synergistic, but these are not well understood, and it is not clear if they are considered in clinical practice. Studies that explicitly compare drugs with diet or physical activity or control for drug use found lifestyle could delay or reduce medication, but most people eventually needed to progress onto drug treatment. However, there are few studies that provide strategies for long-term maintenance of weight loss or physical activity.

Conclusion

Diet and physical activity are of key importance in type 2 diabetes management and attention to them improves glycaemic control and cardiovascular disease risk, but it is not yet known whether maintained lifestyle changes provide an alternative to drug therapy in the long term.

Introduction

In the UK, the National Institute for Health and Care Excellence advises that, if HbA1c rises to 48mmol/mol (6.5%), adults with type 2 diabetes should start medication, with metformin as the first-line drug if tolerated [1]. Similarly, the American Diabetes Association and the European Association for the Study of Diabetes advise that drug therapy should be started on diagnosis [2]. The guidelines also indicate that lifestyle management, which includes dietary advice/medical nutrition therapy and physical activity is necessary, but diet and physical activity are presented as an adjunct to drug therapy rather than an alternative.

However, in 2015 the Diabetes UK-James Lind Alliance Priority Setting Partnership in Type 2 diabetes published a list of ten research priorities to highlight unanswered questions and areas of uncertainty [3]. One of the priorities was to ask if diet and exercise should be used as an alternative to drugs in the management of type 2 diabetes or alongside them. This question recognises that people do not find drug therapy straightforward, and that medications can produce side-effects [4]. In contrast diet and physical activity have few side effects [2] and there is evidence that they can reduce or delay the need for medication [5-8]. People with type 2 diabetes and health professionals would like more research on how to decide which approach to treatment is best for each person, recognising that not all people with type 2 diabetes may benefit from drugs or diet or physical activity in the same manner.

This review provides an overview of the literature on diet and physical activity alongside or instead of drug therapy, with a focus on the management of hyperglycaemia with type 2 diabetes prior to insulin initiation. We have taken a broad approach to the topic and have not attempted a systematic review. Instead, we have drawn evidence from systematic and other narrative reviews and relevant randomised controlled trials and cohort studies to ask: 1) What can diet, and physical activity achieve? 2) What is known about interactions between diet or physical activity and drugs? 3) What can diet, and physical activity achieve in comparison with drugs? 4) Should there be an individualised approach for stage, age, gender and ethnicity?

This review does not include detailed examinations of remission of type 2 diabetes through diet or whether there is an ideal macronutrient ratio for type 2 diabetes since these questions have been addressed by other reviews in this series [9, 10].

1) What can diet, and physical activity achieve?

Effect of diet advice on HbA1c

Dietary advice or Medical Nutrition Therapy is the cornerstone of treatment for type 2 diabetes and is an important part of Diabetes Self-Management Education and Support [2, 11]. Figure 1 outlines the benefits that can be achieved with diet and physical activity in people with type 2 diabetes.

There is little evidence for the superiority of one dietary approach over another or for an ideal macronutrient ratio so an individualised approach is recommended [10-12]. There is evidence that high quality dietary advice can improve HbA1c from a systematic review showing that dietary advice given by dietitians can reduce HbA1c by 3mmol/mol to 22mmol/mol (0.3% - 2.0%). For comparison, oral medications are expected to improve HbA1c by around

11mmol/mol (1.0%) [2]. A recent systematic review of behavioural determinants of good glycaemic control found that dietary adherence was the most important determinate [13], reported that the behavioural factor that best predicted HbA1c was dietary adherence (the other behavioural factors included were adherence to physical activity, medications, glucose self-monitoring and appointment keeping.

There is some evidence that specific diets (Mediterranean diet, a low fat vegan diet and a low glycaemic index diet) may improve glycaemic control independently of weight loss [14]. However, there is more evidence that dietary advice for T2D should prioritise weight loss for those who are overweight, and avoidance of weight gain for those of normal weight [11, 12]. A 2015 meta-analysis of 11 lifestyle weight-loss studies [15] found eight that reported a weight loss of <5% at 12months which was associated with an improvement of HbA1c of 2mmol/mol (95% CI, -7 to 2mmol/mol) (0.2% (95% CI: −0.6 to 0.2%)). This is in comparison to two studies where participants achieved a weight loss of ≥5% in the intervention arms. An improvement in HbA1c of 13mmol/mol (95% CI, -15 to 12 mmol/mol) (1.2% (95% CI, -1.4 to -1.1%)) was seen in a Mediterranean diet study, conducted by Esposito et al [16]. The Look Ahead study, the largest randomised controlled lifestyle-based intervention conducted in people with T2D to date, reported an improvement in HbA1c of 7mmol/mol (95% CI, -8 to -7mmol/mol) (0.6% (95% CI, -0.7 to -0.6%)) [17]. Further analysis of Look AHEAD indicated that improvements in HbA1c were greater with greater weight reduction. The Diabetes Remission Clinical Trial (DiRECT) demonstrated that weight loss of 15kg through diet alone can bring about remission of T2D [9].

Other benefits of dietary advice

As well as improving HbA1c, diet can result in other improvements if weight-loss is over 5%. In the Look Ahead study, participants in the intensive lifestyle intervention saw improved lipid control, less sleep apnoea, lower liver fat, improved insulin resistance, less kidney disease and improved quality of life[8]. In the longer term, analysis of data from the Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (ADDITION)-Cambridge found that weight loss of ≥5% in the first year of diagnosis was associated with a 48% lower risk of cardiovascular disease at 10 years (HR 0.52 (95% CI 0.32, 0.86)) [18].

Effect of physical activity on HBA1c

Physical activity, both alone and in combination with dietary advice, has also been observed to lower HbA1c. A 2011 meta-analyses of structured physical activity interventions[19] reported reductions in HbA1c of 7mmol/mol (95% CI, -9 to -5mmol/mol) (-0.7%; 95% CI, to -0.4 to -0.5%), with greater improvements associated with more than 150mins/week structured activity. Physical activity advice alone was not found to improve HbA1c but when given in combination with dietary advice, HbA1c improved by 6mmol/mol (95% CI, -8 to -5mmol/mol) (-0.6%; 95% CI, -0.7 to -0.4%).

Two randomised controlled trials have attempted to clarify what form of supervised exercise is best. In the Diabetes Aerobic and Resistance Exercise trial [20], combined aerobic and resistance produced an additional 5mmol/mol (95% CI, 9 to 1mmol/mol) (0.5% (95% CI, -0.8

to -0.1%) fall in HbA1c compared with the aerobic group and 6mmol/mol (95% CI, -10 to -3mmol/mol) (-0.6 % (95% CI, -0.95 to -0.23%) compared with the resistance group. In people with HbA1c ≤ 58mmol/mol (7.5%), HbA1c only decreased significantly in the combined exercise training group. Church et al [21] also found that when compared with a control group, neither resistance nor aerobic training alone produced a significant change in HbA1c. However, for the combination training exercise group, a fall in HbA1c of 3mmol/mol (0.3%) was seen compared to the control group. Based on this evidence, the American Diabetes Association recommend people with type 2 diabetes undertake at least 150 min per week of moderate to vigorous aerobic exercise with two to three sessions per week of resistance exercise on non-consecutive days [11].

High-intensity interval training (HIT) is the newest form of exercise to be tried in the management of type 2 diabetes–as it takes less time to perform and can produce similar metabolic effects to longer duration of standard exercises. A meta-analysis of four small studies showed that compared with control conditions, in people with type 2 diabetes, HIT decreased HbA1c by 2mmol/mol (0.2%) [22]. HIT was not superior to continuous training at lowering HbA1c, however it did improve fitness to a greater extent. [23].

Other benefits of physical activity

Like diet, regular physical activity can provide additional benefits over and above its effects on HbA1c. Regular physical activity improves blood pressure, lipid control, fitness and vascular function with greater improvements seen with more than 150 minutes/week of activity [24]. A systematic review of reported that evidence from epidemiological and observational studies in patient with type 2 diabetes found strong associations between higher levels of physical activity and reduction in mortality [25]. However, intervention studies found that physical activity improved cardiovascular risk factors, but the increase in activity and the observed improvements did not always persist after active counselling ceased.

2) Interactions between diet, physical activity and drugs.

Interaction between diet and dipeptidyl peptidase-4 (DPP-4) inhibitors

We could find few studies that had a specific aim of examining the interactions between dietary intake and drugs in type 2 diabetes. It has been suggested in a systematic review that acarbose is more effective in people consuming an Eastern diet than a Western diet due to higher starch intake, but it is not clear whether the included studies measured diet [26]. Similarly, no studies have looked at whether the addition of drug therapies impacts on adherence to dietary advice. The type of meal, order in which food is eaten during a meal, timing of meals and speed in which people eat have all been shown to have an effect on GLP-1 plasma concentrations [27]. For this reason, some small studies have tried to determine whether certain nutrients or foods influence the efficacy of diabetes drugs that increase GLP-1 levels.

An increased in dietary fat, especially saturated fat, has been associated with greater deterioration in the HbA1c lowering effect of DPP-4 inhibitors over time [28]. Higher serum levels of a dietary marker that correlates with fish intake (serum eicosapentaenoic acid) has been associated with a greater fall in HbA1c when starting a DPP-4 inhibitor [29].

Interaction of physical activity and drugs

More evidence is available for interactions between physical activity and drugs but again this has tended to concentrate on supervised exercise and has not looked at whether the addition of drug therapy impacts on adherence to exercise advice. Eckstein et al have recently reviewed the interactions between exercise and non-insulin glucose lowering therapies [30]. Table 1 summarises what is known.

Physical activity and drugs that improve insulin resistance

Metformin and thiazolidinediones both work by helping to increase insulin sensitivity. Three randomised controlled trials which looked at the acute effect of metformin in combination with exercise found that although metformin may reduce the fall in glucose during exercise, glucose control over 24 hours was similar to those who exercised without metformin [31-33]. Sub-analysis of data from The Look Ahead Study. found that addition of metformin, in the long-term to intense lifestyle was found to result in no additional improvement in HbA1c [34]. In a study of people newly diagnosed with of type 2 diabetes, pioglitazone enhanced exercise-stimulated skeletal muscle uptake [33]. In a sub-analysis of the Insulin Resistance After stroke study the HbA1c fall over 20 weeks with pioglitazone was independent of self-reported levels of physical activity [35].

Physical activity and drugs that improve insulin secretion

Both sulfonylureas and glinides act by increasing insulin release from pancreatic beta cells. In a number of studies, exercising with sulfonylureas results in a greater fall in glucose driven by higher insulin levels [36-38]. This increases the risk of hypoglycaemia during exercise, particularly if the exercise is continuous low intensity exercise and the starting glucose concentration is low. No studies have looked at the long-term interaction of sulfonylureas and exercise. Little is known about either the acute or chronic interaction of glinides and exercise.

Physical activity and drugs that improve insulin GLP plasma concentrations

GLP-1RA and DPP-4 inhibitors act by increasing GLP-1 plasma concentrations, which in turn stimulate insulin release and inhibit glucagon release from the pancreas. In participants with type 2 diabetes, liraglutide (a GLP1-RA) added to a 16 week exercise programme resulted in a greater fall in HbA1c, weight and blood pressure compared to exercise alone [39].

Physical activity and SGLT-2 inhibitors

The sodium-glucose co-transporter-2 (SGLT-2) inhibitors prevent the re-uptake of glucose in the proximal convoluted tubule of the kidney resulting an increase in urinary glucose excretion. Due to the osmotic effect of glucose this results in significantly more urine being produced over 24 hours, in some cases an increase of just under ½ a litre. These agents also reduce plasma insulin concentrations and increase plasma glucagon levels, increasing the rate

of lipolysis [40]. During exercise, lipolysis is increased further, and fluid is lost which can lead to ketone body formation and the potential risk of ketoacidosis. To date only one human study has looked at the interaction of SGLT-2 and exercise. This study looked at the effect of 12 weeks of exercise training with placebo or SGLT-2 in sedentary euglycaemic overweight obese men and women. It found that lactate levels rose more during acute exercise in the SGLT2 group when compared to the control group. The SGLT-2 group saw less improvement in insulin sensitivity and a worsening of the glucose response to an oral glucose tolerance tests [41]. No studies to date have looked at the effect of exercise on ketone body formation or reduction in HbA1c in people with type 2 diabetes on SGLT-2 inhibitors.

Physical activity and acarbose

Acarbose inhibits alpha glucosidase, reducing the rate at which starch and sucrose are digested and absorbed. This produces a small but clinically significant reduction in blood glucose. In 105 elderly participants (90% men) with type 2 diabetes of <2 years duration reported that participants taking acarbose, with or without other medication, experienced less of a reduction in blood glucose immediately after walking [42]. However, in a 12-week study in 62 participants, the addition of acarbose to physical activity improved HbA1c in comparison with physical activity alone [43].

Overall, interactions between drug therapy and physical activity have been identified but are not well understood. It cannot be assumed that physical activity and drug therapy will be synergistic, and it is vital that these interactions are identified and are considered when new drugs are developed and tested. Interactions between dietary intake and drugs have not yet been investigated in any detail. It is unclear whether potential interactions between physical activity and drugs or diet and drugs is often considered when treatment decisions are made in practice.

3) What can diet, and physical activity achieve in comparison to drugs?

Despite the benefits of diet and physical activity for type 2 diabetes, there appear to be few studies that directly compare lifestyle interventions to drug therapy, particularly in the longer term. Lifestyle studies have been conducted that use changes in glucose lowering medication as a primary outcome or use a pre-determined prescribing protocol and report changes in medication as a secondary outcome. Studies of this type, and those that compared diet and physical activity directly with medication use, of 12 months or greater duration, are summarised below with more detail in a supplementary table (S1).

Studies that have compared diet and physical activity to drugs at diagnosis

Medication initiation was a primary outcome for two long-term (>5years) studies [7, 16, 44]. The UKPDS reported only 8% of participants met treatment targets on diet alone at 9 years [44]. A Mediterranean diet with moderately restricted carbohydrate, that all participants had initiated medication by 8.1 years [7]. In a shorter randomised controlled trial, Andrews et al [5] made changes to medication according to protocol and reported that the intervention groups achieved a greater reduction in HbA1c with fewer glucose lowering drugs. In addition, the Look Ahead study (which did not have a pre-determined protocol for prescribing glucose

lowering medication), found that the intervention group took fewer medications, with a reduction of 14% for glucose lowering medication at 10 years [8].

Studies that have compared diet and physical activity to drugs at later point

Balducci et al [45] and Johansen et al [46] conducted physical activity interventions, in participants with type 2 diabetes of any duration or up to 10yrs respectively. Both studies adjusted medication to meet target levels and found that HbA1c was more likely to improve in the intervention group, whilst medication use decreased. A secondary analysis of the latter study found that participants in the intervention arm were more likely to experience remission[47]. Baptista et al [48] conducted a cohort study of older adults with type 2 diabetes of any duration, to investigate the effects of an exercise programme and found that only participants who were not on medication at all, in this case metformin, showed an improvement in glycaemia.

Other lifestyle studies have observed a reduction in medication use for participants in diet and physical activity interventions compared with standard care or less intensive lifestyle intervention. Notably, a systematic review of moderate and low carbohydrate interventions found that carbohydrate restriction is likely to reduce the need for medication in both the short and longer term (>12 months) [49].

Studies that have looked at adding diet and physical activity onto drugs

The Today study [50] is one of the few studies in young people with type 2 diabetes. Participants aged 10-17yrs were randomly assigned to continued treatment with metformin alone or to metformin combined with rosiglitazone (4 mg twice a day) or a lifestyle-intervention program focusing on weight loss through eating and activity behaviours. The primary outcome was loss of glycaemic control, defined as an HbA1c of at least 64mmol/mol (8%) for 6 months, or starting on insulin. Although participants in the metformin and lifestyle arm had the least gain in weight, there was no difference in glycaemic control between the lifestyle and metformin arm and the metformin only arm. In contrast to this, the metformin and rosiglitazone arm, despite the biggest gain in weight, achieved the best glycaemic control.

Coppell et al [6] described a diet intervention in with HbA1c>53mmol/mol (7.4%), and found HbA1c improved, whilst medication use also decreased. Wisse et al [51] conducted a two year study of physical activity in sedentary adults with type 2 diabetes on insulin, with mean HbA1c>60mmol/mol (7.6%). No difference between the control and intervention group was observed for HbA1c or insulin use at the end of the study, but self-reported increase in physical activity was the same for both groups and may not have been high enough to impact on HbA1c.

There are other interventions in people with poor glycaemic control that do not report on medication use or changes in medication for all participants. Ligtenberg et al [52] recruited 58 adults, aged >55yrs, poorly controlled, despite treatment with oral medication or insulin. The intervention consisted of a 12-week supervised exercise program, followed by 14-weeks unsupervised. There was no difference in HbA1c between groups after the intervention, which may be due to unsupervised physical activity lacking the necessary intensity. Ten

participants in each group were using insulin and two additional participants from the control group started insulin during the study. Changes to oral medication were not reported. The Centro Universitario Ricerca Interdipartimentale Attività Motoria study [53] was an intensive 3 month lifestyle intervention, involving 26 x 90min gym sessions and a nutritional intervention consisting of regular advice sessions with a dietitian. Secondary analysis at 2-year follow up of the cohort of 222 participants with type 2 diabetes found that HbA1c improved the most for people with poor control at baseline (-17 ± 16mmol/mol (-1.6 ± 1.5%), p<0.001) with no change to defined daily doses for antidiabetic drugs (-0.1 ± 0.6, p=0.16).

Overall, there appear to be few interventions that compare lifestyle interventions with drug therapy. In general, most lifestyle interventions do not control the prescription of medication, many do not report on medication use, and drug trials do not report lifestyle changes. Therefore, it is difficult to draw firm conclusions as to how many people, if any, may be able to substitute diet and physical activity for drug therapy in the long term. However, studies do indicate that adding diet or diet and physical activity can be beneficial at later stages of the disease, even when diabetes is poorly controlled on medication.

4) Individualised approach, stage, age, gender and ethnicity

Role of lifestyle at different stages of diabetes management

The literature reviewed indicates that implementing good dietary habits and regular physical activity on diagnosis can delay or reduce the need for medication for a significant proportion of people with type 2 diabetes. Therefore, guidelines to start everyone on medication immediately on diagnosis may not be appropriate. People newly diagnosed with type 2 diabetes should be offered high quality diet and physical activity programmes that have been demonstrated to work in the community as a first line treatment, using proven behavioural strategies.

It is not yet clear if remission achieved through weight loss can be maintained for the rest of an individual's life. Evidence to date from studies of 5 to 10 years duration indicates that most people do require glucose lowering medication eventually. However, reinforcing diet and physical activity advice can improve HbA1c after medication has started, especially in people who are not well controlled. Diet and physical activity should be reinforced at each stage that drugs are considered and should be intensified for those who are unable to reach target on maximum therapy. Adherence to existing medication should be emphasised and health professionals should take time to explore concerns about polypharmacy and the timing of medications around meals.

Does age change how lifestyle should be used?

Many lifestyle interventions are conducted with participants with mean ages of around 55-60yrs, although some have been conducted specifically in older people [48, 53]. The Look Ahead trial found that intensive lifestyle was more effective in older people (>65yrs) and speculated that this may be due to better adherence with the diet and physical activity guidelines [8]. These studies indicate that a focus on lifestyle can help improve HbA1c in all adult age groups, whilst either reducing the need for medication or keeping it unchanged.

However, if people with type 2 diabetes, particularly older people, start exercising, sulfonylureas and glinides should be avoided due to risk of hypoglycaemia.

It appears that adolescents with type 2 diabetes may not benefit from intensive lifestyle in the same manner. Results from the Today study [50] indicate that intensifying drug therapy was more effective than intensifying lifestyle. Furthermore, the failure rates for metformin alone were higher than similar studies in adults [44], which the study authors think is unlikely to be due to adherence but may indicate that there are biological differences in treatment responses. Despite the lack of observed benefit for additional lifestyle, all participants in all three arms received a minimum of 4 hours of diabetes education that included lifestyle advice and were tested to ensure they understood it and there is no evidence that standard diet and physical activity advice is unnecessary.

Does gender or ethnicity change how lifestyle should be used

There appear to be few studies that consider the effect of gender or ethnicity in lifestyle interventions. It is not known whether men and women, or people from different ethnic backgrounds, following the same advice will achieve the same outcomes. For example, menopause may affect the response to drugs or lifestyle in type 2 diabetes and is poorly understood. The Look Ahead study reported little difference amongst people from different ethnicities [8]. The Today study [50] undertook both gender and ethnicity subgroup analysis and found that there was an interaction with drug treatment and gender and ethnicity but not with the addition of lifestyle. At present individually tailored advice, that takes account of cultural and gendered differences is necessary. In future, lifestyle intervention should be powered to examine interactions between gender and ethnicity and physical activity or diet.

Implementation

Type 2 diabetes is a complex condition that requires a commitment to self-care and engagement with life-long treatment that affects personal and social life. Despite available drug therapies, a choice of dietary approaches and an understanding of the benefits of physical activity, only around 30% of people with type 2 diabetes meet treatment targets [13]. Retrospective evaluation of participants in real world, primary care settings, using routinely collected data, found that a diabetes management program tended to stabilise rather than improve weight (0.07 kg, p=0.832) and HbA1c (0.3mmol/mol (0.03%), p=0.657) over 2 ½ years, and that physical activity levels did not change for 70% of participants [54]. Adherence to drug therapy is reported to be poor and people particularly dislike taking multiple medications [4].

It appears that for many people with type 2 diabetes, successes achieved in research interventions are not translating to routine clinical practice. A systematic review of reviews of lifestyle interventions [55] in people at high risk of type 2 diabetes found good evidence that adding social support (eg from family members) to interventions increased effectiveness. In addition, dietary change was found to benefit from providing instruction, establishing self-monitoring, having strategies to prevent relapse and encouraging self-talk. Physical activity benefited from prompting of activity, establishing self-monitoring, individual tailoring of physical activity or counselling, goal setting, time-management strategies and encouraging

self-talk. However, this kind of best practice from research interventions often does not appear to track through into standard care and health professionals may not always be trained in behaviour change techniques.

Conclusions and future directions

We have presented a broad overview of the literature on what diet and physical activity can achieve in the management of type 2 diabetes, how diet and physical activity may interact with drug therapy and what the evidence is for diet and physical activity in comparison with drug therapy. Table 2 provides recommendations for future research.

The available evidence indicates that diet and physical activity are of key importance in type 2 diabetes and attention to them can improve glycaemic control and cardiovascular disease risk at all stages of the disease but may not be an alternative to drug therapy. However, most people with type 2 diabetes do not receive intensive lifestyle support and there is more work needed on how to maintain diet and lifestyle changes and how to provide this support within healthcare systems and wider society.

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Figure legends

Figure 1: Effect of weight loss and regular exercise in type 2 diabetes